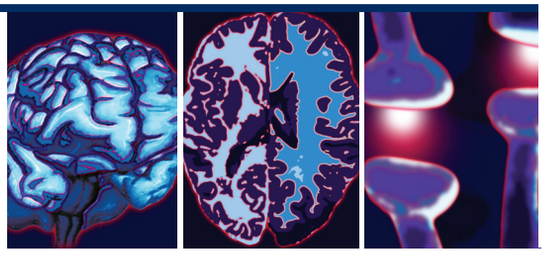
EDITORIAL



Is cannabis responsible for early onset psychotic illnesses?



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Several prospective studies in the general population [1–5] and meta-analyses [6–7] have consistently found that cannabis use is associated with an increased risk of psychotic disorders, in particular schizophrenia. Continued cannabis use over time increases the risk of psychosis in a dose–response fashion [3–5]. A higher risk of schizophrenia is predicted by an earlier age of cannabis use [1,6–7].

Several hypotheses have been suggested to explain the association between cannabis use and schizophrenia, including the following [6,8]:

- Cannabis use is a causal factor for schizophrenia;
- Cannabis use precipitates psychosis in vulnerable people;
- Cannabis use exacerbates symptoms of schizophrenia;
- Patients with schizophrenia are more liable to become regular cannabis users, including during the prodromal phase.

Ferdinand *et al.* investigated the role of pre-existing self-reported psychotic symptoms and found a bidirectional association between cannabis and psychotic symptoms in a 14-year follow-up study in the general population [9]. They showed that cannabis use in individuals who did not have psychotic symptoms before they began using cannabis predicted later psychotic symptoms and that the reverse was also true, in that psychotic symptoms in those who had never used cannabis before the onset of psychotic symptoms also predicted future cannabis use.

However, in a recent 10-year follow-up study, Kuepper *et al.* clarified the temporal association between cannabis use and psychotic experiences by systematically

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addressing the issue of reverse causality [5]. All individuals with pre-existing psychotic experiences or pre-existing cannabis use were excluded. They found that incident cannabis use significantly increased the risk of incident psychotic experiences, independent of age, sex, socioeconomic status, use of other drugs, urban/rural environment, and childhood trauma.

"Age of first exposure to cannabis, dose, genetic factors and sensitivity to the psychotogenic effects of cannabis may be important factors of the earlier onset of psychotic disorders."

Does cannabis use induce an earlier onset of psychotic disorders?

The onset of schizophrenia or the onset of the prodroms of schizophrenia, were found to start earlier in patients with schizophrenia using cannabis compared with non-users in several studies [10–14], albeit not all [15–16]. These discrepancies could be caused by variations in the clinical samples, in particular samples including patients with first-episode psychosis versus samples including patients with schizophrenia, or as a result of confounding effects of other concomitant psychotomimetic drug use. In addition, not all authors agree that the association between cannabis use and earlier age at onset is causal. For instance, according to Sevy *et al.*, there was no significant association between onset of illness and cannabis use disorders that were not accounted for by demographic and clinical variables, in particular the proportion of male subjects among cannabis users [16]. Since older patients with first-episode psychosis are less likely to use cannabis, Wade pointed out that these patients can induce a recruitment bias [17].

Some recent studies clarified the relationships between cannabis use and earlier onset of psychotic disorders, in particular schizophrenia. In a meta-analysis of 83 studies reporting the age at onset of psychotic disorders in cohorts of patients who reported the use of a psychoactive substance compared with the age at onset among a control group of patients with psychosis who did not use psychoactive substances, Large *et al.* found that the age at onset of psychosis for cannabis users was 2.70 years younger, compared with nonusers [18]. By contrast, alcohol use was not significantly associated with a younger age at onset of psychosis. The heterogeneity in the effect sizes between studies may be caused by differences in the proportion of cannabis users in the substance-using group. In addition, the meta-analysis found no evidence that the association between male sex and earlier age at onset of psychosis was the reason for the association between cannabis use and an earlier age of onset [18]. These results were also independent of age inclusion criteria [18].

Which risk factors increase the risk of earlier onset of psychotic disorders in cannabis-using patients?

Early cannabis use

Consistent with previous studies, Leeson *et al.* found that cannabis users with first-episode schizophrenia had an earlier onset of psychotic and prodromal symptoms [14]. Furthermore, they found a strong linear relationship between age at first cannabis use and age at onset of both prodromal and psychotic symptoms [14]. However, Schimmelmann *et al.* found that only cannabis use disorders (CUD) with a starting age of 14 years or younger, were associated with an earlier age at onset of psychosis at a small effect size [19].

Level of misuse of cannabis

Compton *et al.* showed that progression to daily cannabis use was associated with earlier onset of prodromal and psychotic symptoms [11]. In another study of 131 first-episode patients, a gradual reduction in age at onset was observed as the level of misuse of cannabis increased, consisting of a decrement of 7, 8.5 and 12 years for users, abusers, and dependents, respectively, with respect to nonusers [10]. In a study of 116 first-episode patients, the age of onset of schizophrenia correlated with frequency of cannabis use [12].

From another perspective, in a birth cohort of a twin study, McGrath *et al.* demonstrated prospectively that early cannabis use was associated with psychosis-related outcomes in young adults with a dose–response relationship: the longer the duration since first cannabis use, the higher the risk of psychosis-related outcomes [20]. The use of sibling pairs reduces the likelihood that unmeasured confounding factors explain these findings [20].

Genetic & environmental interactions

Some studies suggested the presence of an interaction between genetic and environmental factors involving cannabis and a functional polymorphism in the enzyme catechol-*O*-methyltransferase so that cannabis users with the Val/Val catechol-*O*-methyltransferase genotype were at greater risk for developing psychosis and have a significantly younger age of onset than people with Met/Met or Val/Met alleles [13,21–22].

■ Sensitivity to the psychotogenic effects of cannabis

The individual sensitivity to the psychotogenic effect of cannabis might influence the age of onset of psychosis. In a recent study, we found that among schizophrenia patients with lifetime cannabis use, 36% were characterized as cannabis-sensitive patients (i.e., if the onset of psychotic symptoms occurred within 1 month following the initiation of cannabis consumption, or following a marked rise of cannabis consumption or marked aggravation of psychotic symptoms each time the subject uses cannabis) [15]. Although the age at onset of psychosis was not different in patients with lifetime cannabis use compared with nonusers, the first psychotic episode occurred 2.6 years earlier in cannabis-sensitive patients compared with non-cannabis-sensitive patients [15].

How can cannabis increase the risk of earlier onset of psychotic disorders?

The biological mechanisms whereby cannabis increases the risk of earlier onset of psychosis remains poorly understood. As stressed by Kuepper *et al.*, cannabis use could increase the risk for psychotic illness by increasing the subthreshold psychotic experiences, which would have remained a transitory phenomena for most people without exposure to cannabis [5,23].

Cannabis use could shorten psychotic illnesses by interacting with endophenotypes of schizophrenia, for instance neurological soft signs (NSS) or cognitive dysfunctions. In a recent study, we found that, in a group of subjects seeking treatment for CUD in whom psychosis and a family history of psychosis have been excluded, cannabis dependence was associated with more NSS, especially motor coordination and sensory integration signs [24]. NSS are nonlocalizing subtle neurological abnormalities and include poor motor coordination, sensory perceptual difficulties and difficulties in sequencing of complex motor tasks. These results suggest that cannabinoids interact with the brain networks underlying NSS, known to be altered in schizophrenia.

Cannabis exposure is associated with a decline in cognitive performance in adolescents without psychosis among the general population [25] and could increase the risk of earlier onset of psychosis through cognitive dysfunctions [26]. However, some case–control studies and a meta-analysis showed that regular cannabis use was associated with improved cognitive functioning in patients with schizophrenia [27]. According to Yucel *et al.*, the association between better cognitive performance and cannabis use in schizophrenia may actually be driven by a subgroup of 'neurocognitively less impaired' patients, with a better premorbid adjustment, who only developed psychosis after the starting age of cannabis use (16 years or younger) [27].

Moreover, in a longitudinal study, Leeson *et al.* found that cannabis users with schizophrenia exhibited better cognitive function at psychosis onset (i.e., higher current IQ, better verbal learning, working memory span and planning ability) than never-users and there were no differential group changes in cognition over the following 15 months [14]. They suggested that the group differences in cognition reflect higher intellectual functioning in the cannabis users prior to psychosis onset.

Δ-9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis, can trigger psychosis via direct neurotoxic effects, by alterating dopamine activity, or by other changes in neurotransmission [26]. Cannabis interferes with the endocannabinoid system through specific cannabinoid (CB1) receptors, known to be involved in neuromodulation and neurodevelopment, especially during adolescence [26,28]. Cannabis exposure could disrupt the last steps of brain maturation, enhancing the risk of psychosis [19]. Therefore, the timing of the initiation of cannabis use may be crucial in later schizophrenic disorders. However, the age range of onset of deleterious effects of cannabis use is not precisely known (12–15 years of age) [19].

Activation of CB1 receptors inhibits pre-synaptic neurotransmitter release and consequently modulates the release of neurotransmitters including glutamate, norepinephrine and dopamine. Dopamine plays a key role in the emergence and experience of positive, negative and cognitive symptoms in schizophrenia [23]. THC increases dopamine release in the human striatum [26,29]. A process of sensitization could underlie emergence of psychotic experiences [5,23]. Sensitization refers to a phenomenon, in which repeated exposure to a stressor leads to progressively greater responses over time.

On the other hand, the lower CB1 receptor expression found in schizophrenia could be compensatory to the deficit in perisomatic GABA inputs [30,31]. Exposure to exogenous cannabinoids would counteract these compensatory responses [30,31].

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Conclusion & future perspective

Increased risk of the earlier onset of psychotic disorders associated with cannabis use is now well established. Age of first exposure to cannabis, dose, genetic factors and sensitivity to the psychotogenic effects of cannabis may be important factors of the earlier onset of psychotic disorders. Cannabis use can also interact with other factors (i.e., childhood sexual abuse [32]) to increase the risk. However, the precise biological mechanisms underlying this risk remain unclear.

Further studies are now needed to assess the role of high-potency cannabis preparations (e.g., skunk), which contain between 12 and 18% THC and are found more frequently in first-episode psychosis compared with controls [33]. Further studies are now needed to assess the role of cannabidiol, which could be neuroprotective. Finally, what could be the role of personality traits? We found that in a group of patients with schizophrenia, mean scores on the Barratt Impulsivity Scale and Sensation Seeking Scale are higher in patients with lifetime CUD than in patients without CUD, independent of age, gender or other differences in clinical characteristics of the subsample [34].

Since earlier onset of schizophrenic disorders generally induces increased severity of functional disability, more severe symptoms and behavioral deterioration and less responsiveness to antipsychotics, preventive measures regarding cannabis use are crucial in vulnerable subjects.

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